

# Immunogenicity and Reactogenicity of 13-Valent Pneumococcal Conjugate Vaccine Among Infants, Toddlers, and Children in Western Burkina Faso: Results From a Clinical Trial of Alternative Immunization Schedules

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**Background.** Many African countries have introduced pneumococcal conjugate vaccine (PCV) into their routine immunization program to reduce the burden of morbidity and death that results from *Streptococcus pneumoniae* infection, yet immunogenicity and reactogenicity data from the region are limited for the 2 available PCV products.

**Methods.** We conducted a randomized trial of 13-valent PCV (PCV13) in Bobo-Dioulasso, Burkina Faso. Infants received 3 doses of PCV at 6, 10, and 14 weeks of age or at 6 weeks, 14 weeks, and 9 months of age; toddlers received 2 doses 2 months apart or 1 dose beginning at 12 to 15 months of age; and children received 1 dose between 2 and 4 years of age. We measured each participant's serotype-specific serum immunoglobulin G concentration and opsonophagocytic activity before and after vaccination. For each age group, we compared immune responses between study arms and between the standard schedule in our study and the PCV13-licensing trials.

**Results.** In total, 280 infants, 302 toddlers, and 81 children were assigned randomly and underwent vaccination; 268, 235, and 77 of them completed follow-up, respectively. PCV13 resulted in low reactogenicity in all the study arms. The vaccine elicited a strong primary immune response in infants after 2 or more doses and in children aged 1 to 4 years after 1 dose. Infants who received a booster dose exhibited a robust memory response. Immunogenicity was higher than or comparable to that observed in the PCV13-licensing trials for a majority of serotypes in all 3 age groups.

**Conclusions.** PCV13 has a satisfactory immunogenicity and reactogenicity profile in this population. Our findings will help support decision making by countries regarding their infant and catch-up vaccination schedules.

**Keywords:** immunization schedules; immunogenicity; meningitis belt; pneumococcal conjugate vaccine.

Burkina Faso is located at the heart of the African meningitis belt and experiences hyperendemic bacterial meningitis during the dry season (November through April) of each year; large-scale epidemics occur every 4 to 6 years [1–4]. During interepidemic periods, a substantial proportion of meningitis cases are caused by *Streptococcus pneumoniae* (pneumococcus) infection, which affects all age groups and is associated with a high case-fatality rate and neurological sequelae [5–8]. Although the

epidemiology and etiology of acute respiratory infections in the region are less well understood, the results of global analyses suggest that pneumonia is the leading cause of death in children younger than 5 years, and one-quarter to one-third of fatal cases are estimated to have been pneumococcal [9]. Data from surveillance in northern Togo [10] revealed an incidence of children hospitalized for pneumonia that was lower than that reported in the meta-analyses but confirmed the high prevalence of *S pneumoniae* infection among case-patients.

Pneumococcal conjugate vaccines (PCVs) are safe and effective for preventing invasive pneumococcal disease, chest radiograph-confirmed pneumonia, and death in young children [11–14]. The authors of a recent systematic review examined the effect of various dosing schedules on PCV immunogenicity, nasopharyngeal carriage, and other outcomes in clinical trials and observational studies published through 2011 [15–18]. An updated literature search revealed that

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only the 9-valent PCV (PCV9, unlicensed) (Wyeth, Pearl River, New York) and PCV10 (Synflorix, GlaxoSmithKline, Brentford, UK) had been evaluated in clinical trials in Africa (K. L. O'Brien, personal communication), although PCV13 (Prevnar 13, Pfizer, New York, New York) is licensed and has been implemented into routine immunization in many countries in the region. In addition, there are no data from Africa from directly comparing of the alternative infant schedules recommended by the World Health Organization (WHO) (3 primary doses beginning at 6 weeks of age and administered at least 4 weeks apart or 2 primary doses beginning at 6 weeks of age and administered at least 8 weeks apart, followed by a booster dose at 9 months of age or older [19]) or examining of the immunogenicity of 1- or 2-dose schedules in toddlers and older children.

In Togo, surveillance revealed that approximately 80% of laboratory-confirmed cases of pneumococcal disease were caused by a PCV13 serotype [10]; earlier data from the region came primarily from meningitis cases meningitis and revealed a predominance of serotype 1, particularly during outbreaks that affect adolescents and adults, as well as young children [5–8]. As a prelude to a PCV13 impact study in neighboring Togo, we undertook a phase IV randomized controlled trial to evaluate the vaccine's immunogenicity and reactogenicity among infants, toddlers, and children according to several immunization schedules in Burkina Faso. In particular, we aimed to (1) describe the immune response to PCV13 according to age group in the meningitis belt, where natural population exposure to *S pneumoniae* differs from that in other regions, and compare it to data from PCV13 licensure trials and (2) compare the immunogenicity of alternative vaccination schedules in infancy. This trial was registered at ClinicalTrials.gov (identifier NCT01577771).

## METHODS

### Study Description

This study was a randomized controlled open-label trial evaluating the immunogenicity and reactogenicity of PCV13 in 3 age groups, namely, (1) infants enrolled at 42 to 56 days of age and randomly assigned to receive vaccine at 6 weeks, 14 weeks, and 9 months of age (group A, 2 + 1 schedule) or at 6, 10, and 14 weeks of age (group B, 3 + 0 schedule), (2) toddlers enrolled at 12 to 15 months of age and randomly assigned to receive 1 dose of vaccine (group C) or 2 doses with a 2-month interval between doses (group D), and (3) children enrolled at 2 to 4 years of age, who received 1 dose of PCV (group E). PCVs were not available in Burkina Faso at the time of the trial.

### Patient Enrollment

Each infant was identified shortly after birth or at his or her first clinic visit at 1 of 3 primary health care facilities in

Bobo-Dioulasso. Infants eligible for inclusion ([Supplementary Text](#)) were enrolled and asked to return for their first study visit at 6 weeks of age. During this visit, study staff conducted a basic clinical examination on each participant, assigned him or her to a study arm using the prepared randomization envelope, and administered routine and study immunizations.

Toddlers and children were recruited at their home using a 2-stage cluster-randomized sampling approach. We randomly selected 10 of the 23 residential sectors of Bobo-Dioulasso and 10 intersections within each sector. From these intersections, field workers randomly identified the first household to be visited. In each household, field workers compiled a list of eligible children and randomly selected up to 2 children per age group for inclusion. Participants were then invited to the Centre Muraz clinic for a basic clinical examination, random assignment (toddlers only), and vaccination.

### Randomization

Randomization was performed in blocks of 20 using a Stata random-number-generator function based on the uniform probability distribution after stratifying according to clinic (infants only).

### Reactogenicity Assessment

PCV (lot number A08824-001L01) was administered intramuscularly into the anterolateral left thigh. In the infant group, all concomitant vaccines were administered into the right thigh. During each vaccination visit, participants remained under observation for 30 minutes after PCV administration to enable assessment of any immediate adverse reactions. Field workers then visited the participants' home on days 1 and 3 after each dose and recorded adverse effects using a standardized questionnaire. Fever was defined as an oral temperature of  $\geq 38^{\circ}\text{C}$ , as measured by a field worker at the time of the home visit. Severe adverse events (SAEs) were identified at local hospitals and clinics and through parental reports and were reported to Pfizer within 48 hours. The study pharmacovigilance committee met monthly to review all SAEs and perform causality evaluations.

### Immunogenicity Assessment

Venous blood was collected at the 6-week, 18-week, 9-month, and 10-month visits for infants; at baseline and 3 months after baseline for toddlers; and at baseline and 1 month after baseline for children. Blood was inoculated into a serum-separator tube and transported to the laboratory in a cool box within 8 hours of collection. At the laboratory, blood was centrifuged, aliquoted, and stored at  $-80^{\circ}\text{C}$  until shipment to Pfizer laboratories for immunoglobulin G (IgG) and opsonophagocytic activity (OPA) testing. We used an enzyme-linked immunosorbent assay to test serotype-specific serum IgG levels for the 13 vaccine-type capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and measured functional

antibodies in a multiplexed opsonophagocytic assay as previously described [20]. OPA values are expressed as an opsonophagocytic antibody titer equivalent to the reciprocal of the serum dilution needed to produce 50% killing of the relevant serotype.

#### Ethical Considerations

The study protocol was reviewed and approved by the Centre Muraz Institutional Review Board (Comité d'Ethique Institutionnel), the Burkina Faso National Ethical Review Committee (Comité d'Ethique pour la Recherche en Santé), and the Burkina Faso National Regulatory Authority (Direction Générale de la Pharmacie, des Laboratoires et du Médicament). It also received a positive opinion from a French ethical review committee (Comité de Protection des Personnes de Saint Germain en Laye) and from the French National Data Protection Committee (Commission Nationale Informatique et Libertés). All study activities were conducted according to the International Conference on Harmonization good clinical practice guidelines.

#### Sample-Size Calculation and Data Analysis

In the infant group, we estimated a sample size of 140 per group to have 80% power to compare the proportions of participants with a serotype-specific IgG level of  $\geq 0.35 \text{ } \mu\text{g/mL}$  (the accepted correlate of protection for invasive pneumococcal disease [21]) after 2 or 3 primary doses, assuming at least 80% response in the 3-dose group, 20% loss to follow-up, a noninferiority margin of 0.15, and a 1-sided significance level of .025. In the toddler group, the sample size was 180 per group for a comparison of the proportions of participants with an IgG level of  $\geq 0.35 \text{ } \mu\text{g/mL}$  after 1 or 2 doses, assuming at least 92.7% response in the 2-dose group (based on the least immunogenic serotype from the PCV13-licensing trial in Poland), 10% loss to follow-up, a design effect of 1.5, and a noninferiority margin of 0.1 with the same power and significance levels. In the child group, we aimed to enroll 115 participants to compare the proportion of participants with an IgG level of  $\geq 0.35 \text{ } \mu\text{g/mL}$  to that observed in the PCV13-licensing trial in Poland, assuming an 88.1% response rate for the least immunogenic serotype, 5% loss to follow-up, a design effect of 1.5, and a noninferiority margin of 0.15 with the same power and significance levels.

The primary analysis was intention to treat and included all participants with serum available for testing, irrespective of the vaccine schedule received. We calculated serotype-specific IgG geometric mean concentrations (GMCs) and OPA geometric mean titers (GMTs) and evaluated the percentage of participants with an IgG level of  $\geq 0.35 \text{ } \mu\text{g/mL}$ . We compared the immune response for infant groups A and B using *t* tests for means and  $\chi^2$  tests for proportions and setting a cutoff of .05 for statistical significance. We did not directly compare toddler

groups C and D, because blood was not drawn at the same time point for the 2 groups (3 months after vaccination in group C and 1 month after vaccination in group D).

## RESULTS

#### Study Participants

##### *Infants*

A total of 304 infants were enrolled between March 4 and August 13, 2013, of which, 280 were randomly assigned, underwent a blood draw, and received vaccine and 268 completed follow-up to 10 months of age (Supplementary Figure 1a). Infants in groups A and B were similar in terms of sex, weight at birth, weight and height at first immunization visit, maternal education, and vaccination clinic (Table 1).

##### *Toddlers Aged 12 to 15 Months*

A total of 492 toddlers were enrolled between July 1 and December 12, 2013, of which, 302 (62% of those enrolled) were randomly assigned, underwent a blood draw, and received vaccine and 242 (80% of those randomly assigned) completed follow-up and underwent a final blood draw (Supplementary Figure 1b). Groups C and D were similar in terms of sex, age, weight, and height at the time of their visit and maternal education (Table 2).

##### *Children Aged 2 to 4 Years*

A total of 127 subjects were enrolled between July 1 and October 23, 2013, of which, 81 underwent a blood draw and received vaccine and 78 completed follow-up and underwent a final blood draw (Supplementary Figure 1c).

#### PCV13 Reactogenicity

Supplementary Tables 1–14 provide detailed descriptions of PCV13 reactogenicity according to study group, dose, and time since immunization. Systemic and local adverse effects were

**Table 1. Basic Characteristics of Infant Study Participants**

Characteristic	Group A (n = 140)	Group B (n = 140)	P(Group A vs B)
Female sex (n [%])	66 (47.1)	70 (50.0)	.61
Birth weight (mean [SD]) (kg)	3.09 (0.37)	3.05 (0.34)	.27
Weight at N1 (mean [SD]) (kg)	4.69 (0.59)	4.60 (0.57)	.20
Height at N1 (mean [SD]) (cm)	55.1 (2.3)	55.0 (2.2)	.92
Maternal education (n [%])			
None	79 (56.4)	64 (45.7)	.31
Primary	40 (28.6)	24 (35.7)	
Secondary	20 (14.3)	25 (17.9)	
Tertiary	1 (0.7)	1 (0.7)	
Clinic (n [%])			
Accart Ville	50 (50)	50 (50)	.99
Farakan	50 (50)	50 (50)	
Guimbi	40 (50)	40 (50)	

Abbreviations: N1, 6-week visit; SD, standard deviation.

**Table 2. Basic Characteristics of Toddler Study Participants**

Characteristic	Group C (n = 153)	Group D (n = 149)	P(Group C vs D)
Female sex (n [%])	81 (52.3)	74 (50.0)	.69
Age at T1 (mean [SD]) (mo)	13.90 (1.20)	13.96 (1.20)	.63
Weight at T1 (mean [SD]) (kg)	9.15 (10.01)	9.20 (8.79)	.67
Height at T1 (mean [SD]) (cm)	76.8 (3.2)	77.0 (2.9)	.51
Maternal education (n [%])			
None	80 (52.3)	73 (49.3)	.61
Primary	31 (20.3)	36 (24.3)	
Secondary	41 (26.8)	36 (24.3)	
Tertiary	1 (0.7)	3 (2.0)	

<sup>a</sup>Abbreviations: T1, first clinic visit; SD, standard deviation.

rare on day 1 after vaccination and did not persist more than 48 hours. They were more common in infants than in toddlers or older children.

We recorded 8 SAEs among the infants (1 in group A, 7 in group B), 5 among the toddlers (3 in group C, 2 in group D), and 1 among the children. The study pharmacovigilance committee determined that none of the SAEs were causally related to the PCV vaccination.

## PCV13 Immunogenicity

### Infants

Participants in the 2 infant study arms had similar serotype-specific IgG GMCs at baseline, and the highest levels of antibody were observed for serotypes 6A, 14, and 19A (Tables 3–5 and Figure 1). Infants in both groups displayed a strong primary immune response to all serotypes included in the vaccine and experienced antibody waning between the post-primary series and prebooster time points. Infants who received a booster dose exhibited a robust anamnestic response.

After the primary series, the 2-dose group had significantly lower IgG GMCs than the 3-dose group for 9 of 13 serotypes (Tables 3 and 4) and had a lower proportion of participants with an IgG level of  $\geq 0.35 \mu\text{g/mL}$  for serotypes 3, 6B, 14, 18C, and 23F (Table 5) ( $P < .01$  for all comparisons). Before the booster, differences in IgG GMCs between the 2-dose and 3-dose groups were significant for 5 of 13 serotypes, and differences in the proportions of subjects with an IgG level of  $\geq 0.35 \mu\text{g/mL}$  were significant for serotypes 4, 6B, 14, 18C and 23F.

After 3 doses, the 2 + 1 schedule produced higher IgG levels than the 3 + 0 schedule for 9 of 13 serotypes and lower IgG levels for serotype 3, which translated into differences

**Table 3. Serotype-Specific IgG GMCs in the Infant Cohort According to Study Arm and Blood Draw Time Point**

Group	Serotype	N	Baseline			After Primary Series			At 9 months			At 10 months					
			GMC	95% CI	P <sup>a</sup>	N	GMC	95% CI	P	N	GMC	95% CI	P	N	GMC	95% CI	P
A	1	133	0.10	0.08–0.12		136	3.30	2.77–3.93		133	0.59	0.52–0.66		135	6.34	5.37–7.48	
	3	134	0.07	0.06–0.08		135	0.77	0.68–0.88		125	0.09	0.07–0.11		129	0.61	0.52–0.73	
	4	135	0.08	0.06–0.09		136	3.17	2.68–3.74		134	0.45	0.38–0.53		135	4.53	3.86–5.31	
	5	131	0.31	0.26–0.36		136	1.26	1.08–1.48		134	0.63	0.55–0.73		135	3.5	3.04–4.03	
	6A	137	0.86	0.75–0.98		136	2.01	1.7–2.38		133	0.8	0.69–0.92		135	6.55	5.45–7.89	
	6B	135	0.29	0.24–0.35		136	0.92	0.72–1.18		132	0.52	0.43–0.62		135	9.83	8.20–11.77	
	7F	137	0.17	0.14–0.21		136	3.66	3.16–4.25		133	0.89	0.78–1.02		135	5.77	4.99–6.68	
	9V	139	0.30	0.26–0.36		136	1.49	1.28–1.72		134	0.39	0.34–0.45		135	3.01	2.61–3.49	
	14	139	1.03	0.83–1.28		135	2.23	1.75–2.84		133	1.14	0.90–1.44		133	8.12	6.64–9.93	
	18C	134	0.19	0.16–0.23		135	1.66	1.34–2.07		134	0.26	0.22–0.31		135	2.9	2.45–3.43	
	19A	139	0.74	0.63–0.88		136	2.82	2.29–3.46		134	0.71	0.59–0.87		135	6.15	5.12–7.39	
	19F	133	0.33	0.27–0.41		135	6.92	5.81–8.24		133	0.89	0.75–1.07		133	8.64	7.18–10.4	
	23F	136	0.30	0.25–0.36		136	1.11	0.89–1.39		132	0.24	0.19–0.29		135	4.19	3.40–5.17	
B	1	135	0.09	0.07–0.11	.40	135	3.15	2.73–3.63	.69	134	0.68	0.58–0.8	.17	133	0.60	0.51–0.69	<.01
	3	135	0.06	0.05–0.08	.69	135	1.69	1.51–1.89	<.01	124	0.15	0.12–0.19	<.01	122	0.13	0.10–0.17	<.01
	4	137	0.07	0.06–0.09	.71	135	4.79	4.22–5.44	<.01	134	0.65	0.56–0.75	<.01	133	0.54	0.46–0.63	<.01
	5	137	0.30	0.25–0.36	.84	134	1.31	1.13–1.53	.72	133	0.67	0.57–0.79	.57	131	0.74	0.63–0.87	<.01
	6A	136	0.95	0.84–1.08	.26	135	2.17	1.89–2.5	.48	134	0.76	0.67–0.87	.68	132	0.80	0.69–0.92	<.01
	6B	134	0.29	0.24–0.36	.88	135	3.40	2.65–4.36	<.01	134	0.67	0.56–0.81	.05	132	0.68	0.55–0.83	<.01
	7F	137	0.15	0.13–0.19	.45	135	3.42	3.08–3.79	.45	134	0.9	0.79–1.03	.89	133	0.84	0.73–0.96	<.01
	9V	138	0.28	0.23–0.33	.49	135	2.46	2.18–2.77	<.01	134	0.46	0.40–0.54	.11	133	0.45	0.38–0.54	<.01
	14	139	0.79	0.62–1.00	.11	135	4.28	3.55–5.17	<.01	134	2.54	2.05–3.15	<.01	133	2.23	1.79–2.77	<.01
	18C	136	0.19	0.16–0.22	.96	135	3.06	2.65–3.54	<.01	134	0.37	0.32–0.43	<.01	133	0.35	0.30–0.42	<.01
	19A	139	0.70	0.59–0.84	.65	134	5.95	5.09–6.95	<.01	134	0.89	0.73–1.07	.13	133	0.91	0.74–1.12	<.01
	19F	136	0.29	0.23–0.35	.34	134	4.75	4.23–5.35	<.01	132	0.74	0.62–0.88	.15	132	0.65	0.54–0.79	<.01
	23F	137	0.28	0.22–0.34	.54	135	2.64	2.25–3.1	<.01	134	0.35	0.28–0.42	.01	131	0.36	0.29–0.46	<.01

Abbreviation: CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G.

<sup>a</sup>P values are for differences in GMCs between groups A and B.

**Table 4. Ratios of Serotype-Specific IgG GMCs for Group A Versus B According to Blood Draw Time Point<sup>a</sup>**

Serotype	Baseline			After Primary Series			At 9 months			At 10 months			After Dose 3 <sup>b</sup>		
	Ratio	95% CI	P	Ratio	95% CI	P	Ratio	95% CI	P	Ratio	95% CI	P	Ratio	95% CI	P
1	1.13	0.9–1.5	.40	1.05	0.8–1.3	.69	0.87	0.7–1.1	.17	10.63	8.5–13.3	<.01	2.01	1.6–2.5	<.01
3	1.06	0.8–1.4	.69	0.46	0.4–0.5	<.01	0.57	0.4–0.8	<.01	4.64	3.4–6.3	<.01	0.36	0.3–0.4	<.01
4	1.05	0.8–1.4	.71	0.66	0.5–0.8	<.01	0.70	0.6–0.9	<.01	8.42	6.7–10.5	<.01	0.94	0.8–1.2	.58
5	1.03	0.8–1.3	.84	0.96	0.8–1.2	.72	0.94	0.8–1.2	.57	4.71	3.8–5.8	<.01	2.66	2.2–3.3	<.01
6A	0.90	0.8–1.1	.26	0.92	0.7–1.1	.48	1.04	0.9–1.3	.68	8.20	6.5–10.4	<.01	3.01	2.4–3.8	<.01
6B	0.98	0.7–1.3	.88	0.27	0.2–0.4	<.01	0.77	0.6–1	.05	14.51	11–19.1	<.01	2.89	2.1–3.9	<.01
7F	1.11	0.9–1.5	.45	1.07	0.9–1.3	.45	0.99	0.8–1.2	.89	6.91	5.7–8.4	<.01	1.69	1.4–2.0	<.01
9V	1.09	0.9–1.4	.49	0.61	0.5–0.7	<.01	0.84	0.7–1	.11	6.66	5.3–8.3	<.01	1.23	1.0–1.5	.04
14	1.31	0.9–1.8	.11	0.52	0.4–0.7	<.01	0.45	0.3–0.6	<.01	3.65	2.7–4.9	<.01	1.90	1.4–2.5	<.01
18C	1.01	0.8–1.3	.96	0.54	0.4–0.7	<.01	0.71	0.6–0.9	<.01	8.20	6.5–10.4	<.01	0.95	0.8–1.2	.62
19A	1.06	0.8–1.4	.65	0.47	0.4–0.6	<.01	0.81	0.6–1.1	.13	6.76	5.1–8.9	<.01	1.03	0.8–1.3	.79
19F	1.15	0.9–1.5	.34	1.46	1.2–1.8	<.01	1.21	0.9–1.6	.15	13.28	10.1–17.4	<.01	1.82	1.5–2.3	<.01
23F	1.09	0.8–1.4	.54	0.42	0.3–0.6	<.01	0.69	0.5–0.9	.01	11.52	8.4–15.7	<.01	1.59	1.2–2.1	<.01

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G.

<sup>a</sup>The sample size used for each time point is the smallest of the sample sizes in groups A and B, as reported in Table 3.<sup>b</sup>"After dose 3" refers to the post-booster dose blood draw for group A and post-primary series blood draw for group B.

in the proportions of infants who achieved the protective threshold for only serotypes 3 (3+0 better than 2+1) and 5 (2+1 better than 3+0) ( $P <.01$  for both comparisons) (Table 3–5).

Antibody functionality assessments yielded similar results (Supplementary Tables 15 and 16). After 3 doses, infants in the 2 + 1 arm had significantly higher OPA GMTs than those in the 3 + 0 arm for serotypes 1, 5, 7F, 9V, and 19A.

**Table 5. Proportions of Infants With a Serotype-Specific IgG Level of  $\geq 0.35 \mu\text{g/mL}$  According to Study Arm and Blood Draw Time Point**

Group	Serotype	Baseline			After Primary Series			At 9 months			At 10 months			After Dose 3 <sup>b</sup> (P) <sup>a</sup>		
		Prop	95% CI	P <sup>a</sup>	Prop	95% CI	P <sup>a</sup>	Prop	95% CI	P <sup>a</sup>	Prop	95% CI	P <sup>a</sup>	Prop	95% CI	P <sup>a</sup>
A	1	0.17	0.10–0.23		0.97	0.94–1.00		0.73	0.65–0.81		0.99	0.96–1.00				
	3	0.07	0.02–0.11		0.89	0.84–0.94		0.14	0.08–0.20		0.78	0.71–0.86				
	4	0.10	0.05–0.15		0.97	0.94–1.00		0.58	0.50–0.67		0.99	0.98–1.00				
	5	0.48	0.39–0.57		0.90	0.85–0.95		0.74	0.66–0.81		0.99	0.98–1.00				
	6A	0.88	0.83–0.94		0.96	0.93–1.00		0.85	0.79–0.91		0.99	0.96–1.00				
	6B	0.48	0.40–0.57		0.72	0.64–0.80		0.66	0.58–0.74		0.98	0.95–1.00				
	7F	0.27	0.19–0.35		0.99	0.96–1.00		0.91	0.86–0.96		0.99	0.98–1.00				
	9V	0.47	0.38–0.55		0.95	0.91–0.99		0.56	0.47–0.64		0.99	0.96–1.00				
	14	0.82	0.76–0.88		0.89	0.84–0.94		0.79	0.72–0.86		0.99	0.96–1.00				
	18C	0.33	0.25–0.41		0.86	0.80–0.92		0.41	0.33–0.49		0.96	0.92–0.99				
	19A	0.79	0.72–0.86		0.96	0.92–0.99		0.75	0.67–0.82		0.99	0.96–1.00				
	19F	0.47	0.39–0.56		0.99	0.98–1.00		0.84	0.78–0.90		0.99	0.96–1.00				
B	23F	0.50	0.41–0.59		0.81	0.74–0.88		0.31	0.23–0.39		0.93	0.89–0.98				
	1	0.16	0.09–0.22	.83	0.98	0.95–1.00	.71	0.82	0.76–0.89	.07	0.75	0.68–0.83	<.01	.65		
	3	0.10	0.05–0.16	.28	0.99	0.96–1.00	<.01	0.19	0.12–0.26	.22	0.17	0.10–0.24	<.01	<.01		
	4	0.09	0.05–0.14	.97	0.99	0.96–1.00	.41	0.81	0.75–0.88	<.01	0.68	0.60–0.76	<.01	.56		
	5	0.47	0.39–0.56	.92	0.91	0.86–0.96	.71	0.78	0.71–0.85	.41	0.77	0.70–0.84	<.01	<.01		
	6A	0.91	0.86–0.96	.44	0.97	0.94–1.00	.74	0.88	0.82–0.94	.46	0.85	0.79–0.91	<.01	.40		
	6B	0.47	0.38–0.56	.85	0.93	0.89–0.98	<.01	0.81	0.74–0.87	.01	0.78	0.71–0.85	<.01	.07		
	7F	0.24	0.17–0.31	.58	1.00	1.00–1.00	.16	0.90	0.84–0.95	.69	0.86	0.81–0.92	<.01	.32		
	9V	0.43	0.35–0.52	.58	0.99	0.96–1.00	.09	0.64	0.56–0.72	.17	0.56	0.47–0.64	<.01	.99		
	14	0.73	0.65–0.80	.06	0.99	0.96–1.00	<.01	0.90	0.84–0.95	.02	0.89	0.84–0.95	<.01	.99		
	18C	0.31	0.23–0.39	.73	0.97	0.94–1.00	<.01	0.55	0.47–0.64	.02	0.49	0.40–0.57	<.01	.53		
	19A	0.72	0.64–0.80	.16	0.99	0.96–1.00	.16	0.83	0.76–0.89	.10	0.81	0.74–0.88	<.01	.99		
	19F	0.43	0.34–0.51	.44	0.99	0.98–1.00	1.00	0.84	0.78–0.90	.98	0.72	0.64–0.80	<.01	.56		
	23F	0.46	0.38–0.54	.51	0.96	0.93–1.00	<.01	0.48	0.39–0.56	.01	0.47	0.39–0.56	<.01	.28		

Abbreviations: CI, confidence interval; IgG, immunoglobulin G; Prop, proportion.

<sup>a</sup>P value for the difference between groups A and B.<sup>b</sup>"After dose 3" refers to the postbooster blood draw for group A and post-primary series for group B.

**Table 6.** Serotype-Specific IgG GMCs in the Toddler Cohort According to Study Arm and Blood Draw Time Point

Group (No. of Doses)	Serotype	Baseline			After Vaccination			Geometric Mean Fold-Rise		
		N	GMC	95% CI	N	GMC	95% CI	N	GMC	95% CI
C (1)	1	139	0.03	0.02–0.03	125	1.32	1.14–1.53	114	52.83	44.36–62.92
	3	131	0.07	0.05–0.09	119	0.59	0.48–0.72	100	7.01	5.32–9.23
	4	93	0.04	0.03–0.05	126	1.31	1.12–1.53	71	33.53	23.19–48.48
	5	124	0.49	0.38–0.63	124	1.71	1.46–2.01	103	3.64	2.8–4.73
	6A	129	0.31	0.26–0.38	126	1.81	1.52–2.14	108	5.81	4.6–7.35
	6B	130	0.11	0.09–0.14	119	0.90	0.72–1.12	99	8.47	6.03–11.9
	7F	148	0.07	0.06–0.09	126	2.69	2.34–3.08	122	36.35	28.54–46.31
	9V	140	0.22	0.16–0.28	125	1.31	1.11–1.55	114	5.83	4.43–7.66
	14	129	0.03	0.02–0.04	126	2.46	2.07–2.93	106	91.72	71.29–118
	18C	140	0.10	0.08–0.13	125	1.87	1.61–2.16	116	18.01	13.65–23.77
	19A	145	0.61	0.49–0.77	126	3.43	2.86–4.11	121	5.93	4.69–7.5
	19F	138	0.06	0.05–0.08	126	2.11	1.68–2.64	112	31.36	24.12–40.78
	23F	132	0.08	0.06–0.11	126	0.81	0.65–1.01	108	9.82	7.33–13.15
D (2)	1	138	0.03	0.03–0.04	109	4.38	3.66–5.25	100	153.93	114.94–206.13
	3	127	0.06	0.05–0.08	105	0.79	0.65–0.96	90	15.02	10.63–21.21
	4	99	0.04	0.03–0.05	109	3.68	3.12–4.35	71	109.15	78.15–152.46
	5	132	0.41	0.32–0.52	109	3.20	2.73–3.75	98	7.96	6.05–10.49
	6A	125	0.34	0.27–0.41	109	6.44	5.33–7.77	92	20.44	14.62–28.59
	6B	129	0.11	0.08–0.14	109	6.23	4.89–7.95	97	58.68	39.32–87.57
	7F	142	0.08	0.06–0.1	109	5.80	5.11–6.59	103	80.53	62.57–103.63
	9V	138	0.20	0.16–0.26	109	2.48	2.14–2.89	101	12.87	9.58–17.3
	14	133	0.04	0.03–0.05	109	7.66	6.5–9.01	99	195.33	144.21–264.58
	18C	132	0.10	0.08–0.13	109	3.24	2.75–3.83	100	30.74	22.46–42.08
	19A	141	0.55	0.44–0.69	109	7.39	6.27–8.72	104	14.63	11.06–19.36
	19F	130	0.06	0.05–0.07	109	8.08	6.51–10.02	96	136.08	99.19–186.68
	23F	122	0.08	0.06–0.1	109	2.87	2.3–3.59	93	34.07	23.69–48.99

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G.

Compared to infants enrolled in the 2 pivotal studies for PCV13 licensure in the United States (vaccinated at 2, 4, and 6 months of age) [22] and Germany (vaccinated at 2, 3, and 4 months of age) [23], infants in the 3 + 0 group in Burkina Faso had an equivalent or higher immune response to both of the pivotal study groups, for all serotypes and endpoints except for serotype 5 (proportions of participants with an IgG level of  $\geq 0.35 \mu\text{g/mL}$ , 0.91 [Burkina Faso], 0.90 [United States], and 0.93 [Germany]) and serotype 14 (GMCs, 4.28  $\mu\text{g}/\text{mL}$  [Burkina Faso], 4.74  $\mu\text{g/mL}$  [United States], and 4.14  $\mu\text{g}/\text{mL}$  [Germany]).

#### Toddlers Aged 12–15 Months

The 2 toddler study arms had similar serotype-specific IgG GMCs at baseline (Tables 6 and 7 and Figure 2). Baseline GMCs were lower in the toddler cohort than in the infant cohort. Toddlers in both groups had a strong primary immune response to the vaccine (IgG geometric mean fold rise,  $\geq 4$  for all serotypes except for serotype 5 [3.6-fold rise in the single-dose arm]). Three months after vaccination, 91% to 100% of participants in the single-dose arm had an IgG level of  $\geq 0.35 \mu\text{g/mL}$  for all serotypes except 3, 6B and 23F. One month after dose 2,  $\geq 95\%$  of participants in the 2-dose arm had an IgG level of  $\geq 0.35 \mu\text{g/mL}$  for all but serotype

3. In the OPA analysis, both study arms achieved a  $\geq 4$ -fold rise in the OPA GMT for all serotypes after vaccination (Supplementary Table 17).

Burkinabé toddlers who received 2 doses of PCV in our trial had higher IgG GMCs than Polish toddlers who received 2 doses using a similar schedule in a prelicensure trial for 8 of 13 serotypes (1, 5, 6A, 6B, 14, 19A, 19F, and 23F) and a lower GMC for 5 serotypes [24]. Serotype 3 was the only serotype for which the lower GMC achieved in Burkina Faso was accompanied by a lower proportion of subjects with an IgG level of  $\geq 0.35 \mu\text{g}/\text{mL}$  after vaccination (proportion with an IgG level of  $\geq 0.35 \mu\text{g}/\text{mL}$  for serotype 3, 0.80 [Burkina Faso] and 1 [Poland]; for all other serotypes, the difference in proportions was  $< 0.03$ ). We were unable to evaluate the statistical significance of these differences.

#### Children Aged 2–4 Years

Children enrolled in the 2- to 4-year-old cohort had high antibody levels at baseline, particularly for serotypes 5, 6A, 6B, 9V, and 19A, for which  $\geq 70\%$  of the participants had an IgG level of  $\geq 0.35 \mu\text{g/mL}$  (Tables 8 and 9 and Figure 3). PCV elicited a 1.7- to 3.9-fold rise in the GMC for these serotypes and a  $\geq 4$ -fold rise for the 8 other serotypes. After vaccination,

**Table 7. Proportion of Toddlers With a Serotype-Specific IgG Level of ≥0.35 µg/mL According to Study Arm and Blood Draw Time Point**

Group (No. of Doses)	Serotype	Baseline		After Vaccination	
		Prop	95% CI	Prop	95% CI
C (1)	1	0.01	0.00–0.03	0.94	0.9–0.98
	3	0.13	0.07–0.19	0.67	0.59–0.76
	4	0.08	0.02–0.13	0.92	0.87–0.97
	5	0.69	0.60–0.77	0.98	0.95–1.00
	6A	0.48	0.39–0.57	0.94	0.90–0.98
	6B	0.25	0.17–0.32	0.81	0.73–0.88
	7F	0.15	0.09–0.21	0.99	0.98–1.00
	9V	0.39	0.30–0.47	0.92	0.87–0.97
	14	0.09	0.04–0.14	0.98	0.95–1.00
	18C	0.21	0.14–0.28	0.98	0.96–1.00
D (2)	19A	0.68	0.60–0.75	0.99	0.98–1.00
	19F	0.08	0.03–0.13	0.91	0.86–0.96
	23F	0.22	0.15–0.29	0.77	0.70–0.84
	1	0.05	0.01–0.09	0.99	0.97–1.00
	3	0.15	0.09–0.21	0.80	0.72–0.88
	4	0.04	0.00–0.08	0.98	0.96–1.00
	5	0.55	0.47–0.64	0.99	0.97–1.00
	6A	0.50	0.42–0.59	0.99	0.97–1.00
	6B	0.25	0.17–0.32	0.97	0.94–1.00
	7F	0.09	0.04–0.14	1.00	1.00–1.00
	9V	0.34	0.26–0.42	0.99	0.97–1.00
	14	0.10	0.05–0.15	1.00	1.00–1.00
	18C	0.23	0.15–0.30	0.98	0.96–1.00

Abbreviation: IgG, immunoglobulin G.

≥95% of the participants had an IgG level of ≥0.35 µg/mL for all serotypes except serotype 3. OPA GMTs increased ≥4-fold after vaccination for all serotypes, including serotypes 7F, 9V,

and 14, for which high preexisting OPA GMTs were found ([Supplementary Table 18](#)).

After 1 dose of PCV13, Burkinabé children had a higher IgG GMC than the Polish children who received 1 dose at the same age in a prelicensure trial for 8 of 13 serotypes (1, 5, 6A, 6B, 14, 19A, 19F, and 23F) and a lower GMC for the other 5 serotypes [24]. As in toddlers, the proportions of children with an IgG level of ≥0.35 µg/mL was markedly different between the groups for serotype 3 only (0.83 in Burkina Faso vs 0.97 in Poland; for all other serotypes, the difference in proportions was <0.05).

## DISCUSSION

This study provides novel data on PCV13 immunogenicity from the African continent and confirms the vaccine's excellent immunogenicity profile in children up to 5 years of age for all of the dosing schedules evaluated. The vaccine elicited a strong primary immune response in infants after 2 or more doses and in children aged 1 to 4 years after 1 dose. Infants who received a booster dose exhibited a robust memory response. Serum IgG levels correlated with OPA, which confirms the functionality of vaccine-induced antibodies.

The immune responses to PCV13 observed in our study, when administered according to the routine infant (6, 10, and 14 weeks) and standard catch-up (2 doses in toddlers aged 12 to 15 months or 1 dose in children aged 2 to 4 years) schedules were broadly comparable to those measured in pivotal prelicensure trials in the United States, Germany, and Poland for all age groups, immunogenicity endpoints, and serotypes. Results of an earlier review of PCV performance, including limited data on PCV13, suggested that PCV immunogenicity was generally higher in Africa than in Europe or North America, possibly because of its coadministration with whole-cell rather

**Table 8. Serotype-Specific IgG GMCs in the Child Cohort According to Study Arm and Blood Draw Time Point**

Serotype	Baseline			After Vaccination			Geometric Mean Fold Rise		
	N	GMC	95% CI	N	GMC	95% CI	N	GMC	95% CI
1	67	0.13	0.09–0.20	78	2.72	2.14–3.46	64	20.06	13.58–29.64
3	70	0.28	0.18–0.44	78	1.11	0.85–1.45	67	3.89	2.72–5.56
4	77	0.07	0.05–0.09	78	3.16	2.40–4.17	73	49.68	35.36–69.79
5	73	1.60	1.21–2.10	78	2.37	1.89–2.97	69	1.57	1.35–1.84
6A	73	1.81	1.44–2.27	78	3.54	2.83–4.42	70	2.17	1.83–2.57
6B	75	1.04	0.73–1.47	76	2.76	2.08–3.68	71	2.53	2.00–3.21
7F	74	0.12	0.09–0.16	78	3.25	2.61–4.04	70	25.38	19.14–33.65
9V	79	0.79	0.58–1.06	78	2.72	2.20–3.36	75	3.42	2.66–4.39
14	80	0.16	0.11–0.25	78	3.36	2.35–4.80	76	19.93	14.68–27.08
18C	78	0.49	0.37–0.65	78	4.06	3.17–5.20	74	8.5	6.31–11.44
19A	80	2.88	2.25–3.69	78	11.33	8.73–14.71	76	3.95	3.07–5.09
19F	74	0.33	0.24–0.46	77	2.47	1.81–3.36	69	7.98	5.92–10.77
23F	73	0.63	0.46–0.87	78	2.28	1.76–2.96	69	3.79	2.93–4.91

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G.

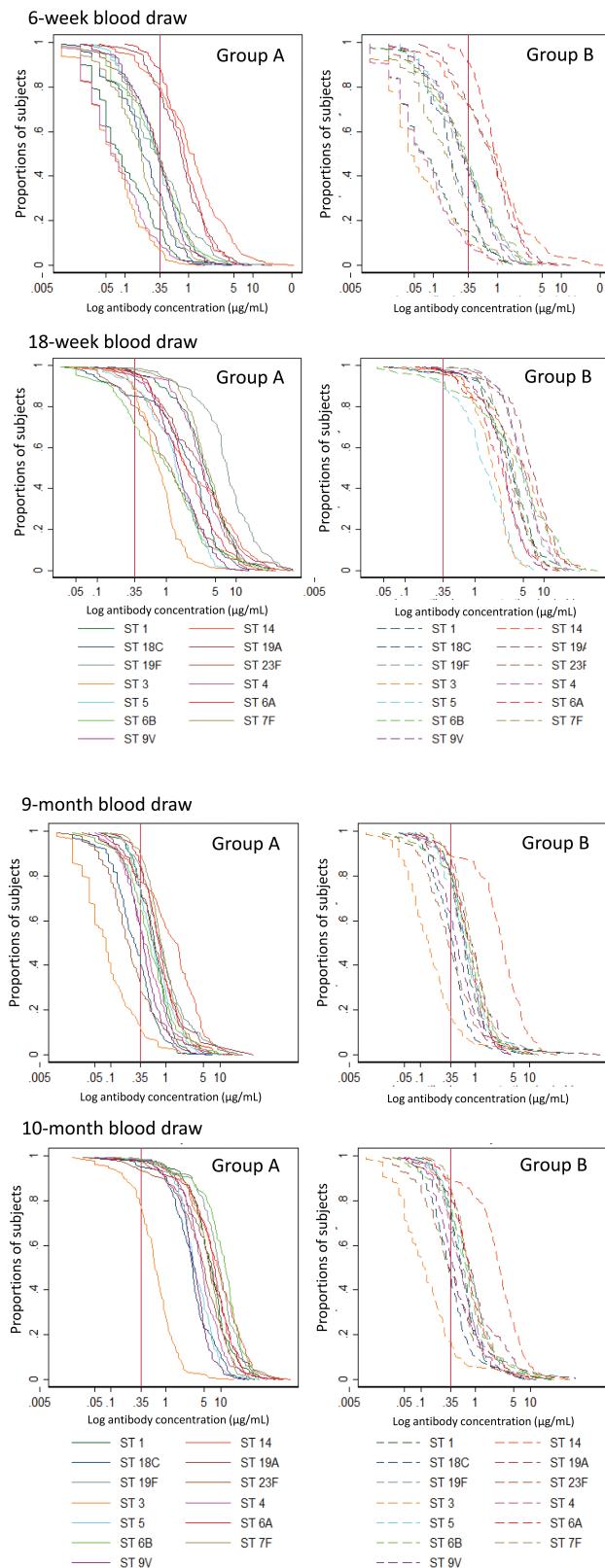
**Table 9. Proportion of Children With a Serotype-Specific IgG Level of  $\geq 0.35 \mu\text{g/mL}$  According to Blood Draw Time Point**

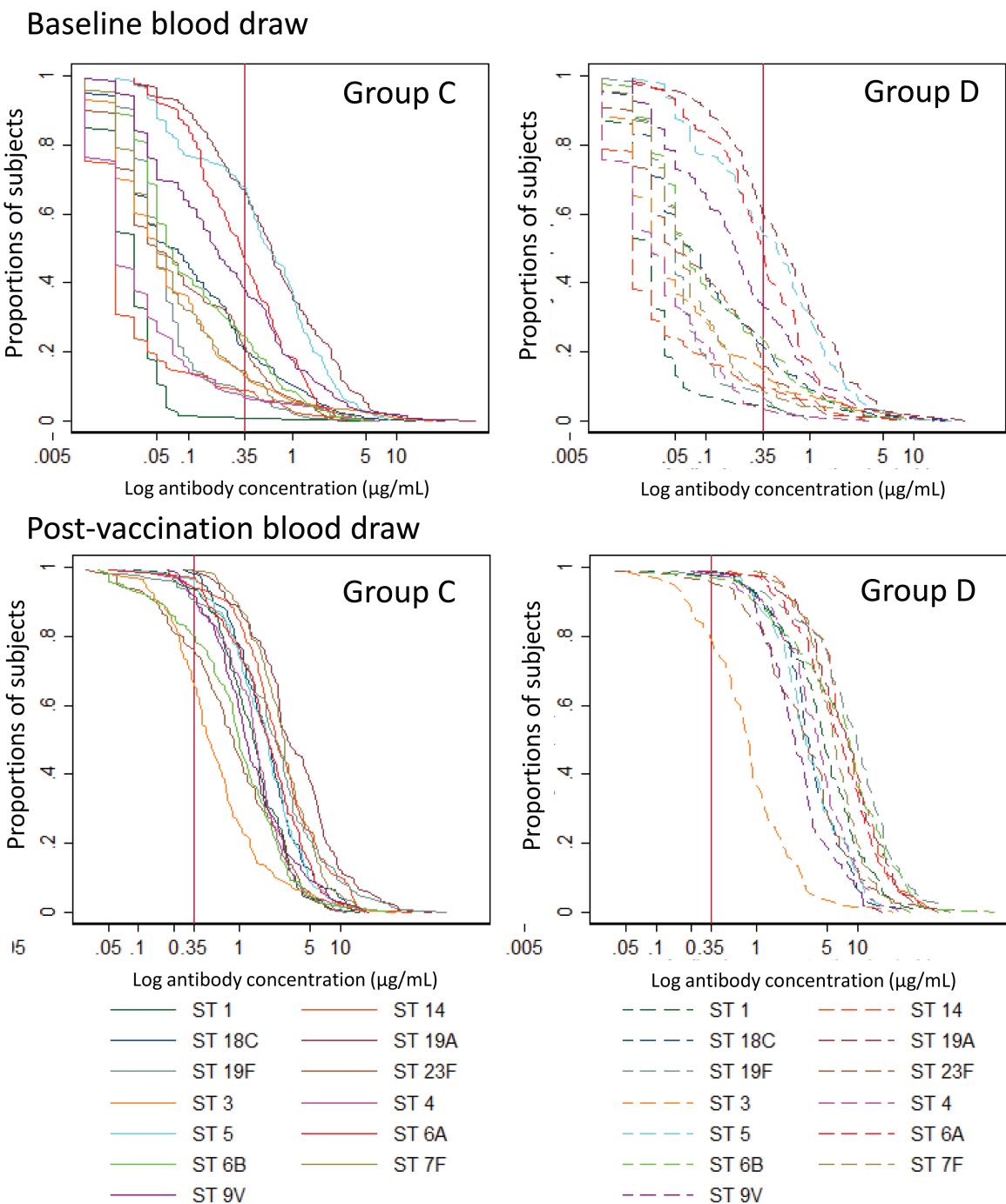
Serotype	Baseline		After Vaccination	
	Prop	95% CI	Prop	95% CI
1	0.25	0.15–0.36	0.97	0.94–1.00
3	0.44	0.32–0.56	0.83	0.75–0.92
4	0.18	0.09–0.27	0.95	0.90–1.00
5	0.90	0.83–0.97	0.97	0.94–1.00
6A	0.95	0.89–1.00	0.97	0.94–1.00
6B	0.79	0.69–0.88	0.95	0.90–1.00
7F	0.15	0.07–0.23	1.00	1.00–1.00
9V	0.71	0.61–0.81	0.97	0.94–1.01
14	0.38	0.27–0.48	0.97	0.94–1.01
18C	0.60	0.49–0.71	0.99	0.96–1.01
19A	0.98	0.94–1.00	1.00	1.00–1.00
19F	0.42	0.30–0.53	0.96	0.92–1.01
23F	0.70	0.59–0.81	0.95	0.90–1.00

Abbreviation: IgG, immunoglobulin G.

than acellular pertussis vaccines [15]. Results of our comparison of infant immune responses to PCV13 across populations only partly support this finding; results among studies and serotypes have varied. In particular, serotype 3 was more immunogenic in infants but less immunogenic in toddlers and children in Burkina Faso than in licensing trial participants. Overall, serotype 3 was poorly immunogenic, as seen in a number of previous studies [22–24].

The WHO recommends that PCV be administered to infants according to either a 3 + 0 (3 primary doses at least 4 weeks apart) or a 2 + 1 (2 primary doses at least 8 weeks apart followed by a booster dose between 9 and 15 months of age) schedule. Countries that decide to introduce PCV are advised to consider the local epidemiology of pneumococcal disease, particularly the peak age of disease, along with programmatic convenience when choosing between these schedules. The majority of African countries have opted for a 3 + 0 schedule. In The Gambia, after introduction of PCV13 into the national immunization program, this schedule resulted in 68% to 82% effectiveness against vaccine-type invasive pneumococcal disease and 20% effectiveness against chest radiograph-confirmed pneumonia [25]. In the meningitis belt, however, the high incidence of invasive pneumococcal disease and high case-fatality rates (40%–60% among all age groups) beyond childhood [26] argue for considering a 2 + 1 schedule, which would likely offer longer-term individual protection. Similarly, the high burden of disease in adolescents and adults with human immunodeficiency virus infection [27] drove South Africa's decision to introduce PCV with a 2 + 1 schedule [28]. The country has since achieved major reductions in disease rates in both vaccinated and unvaccinated age groups [29].

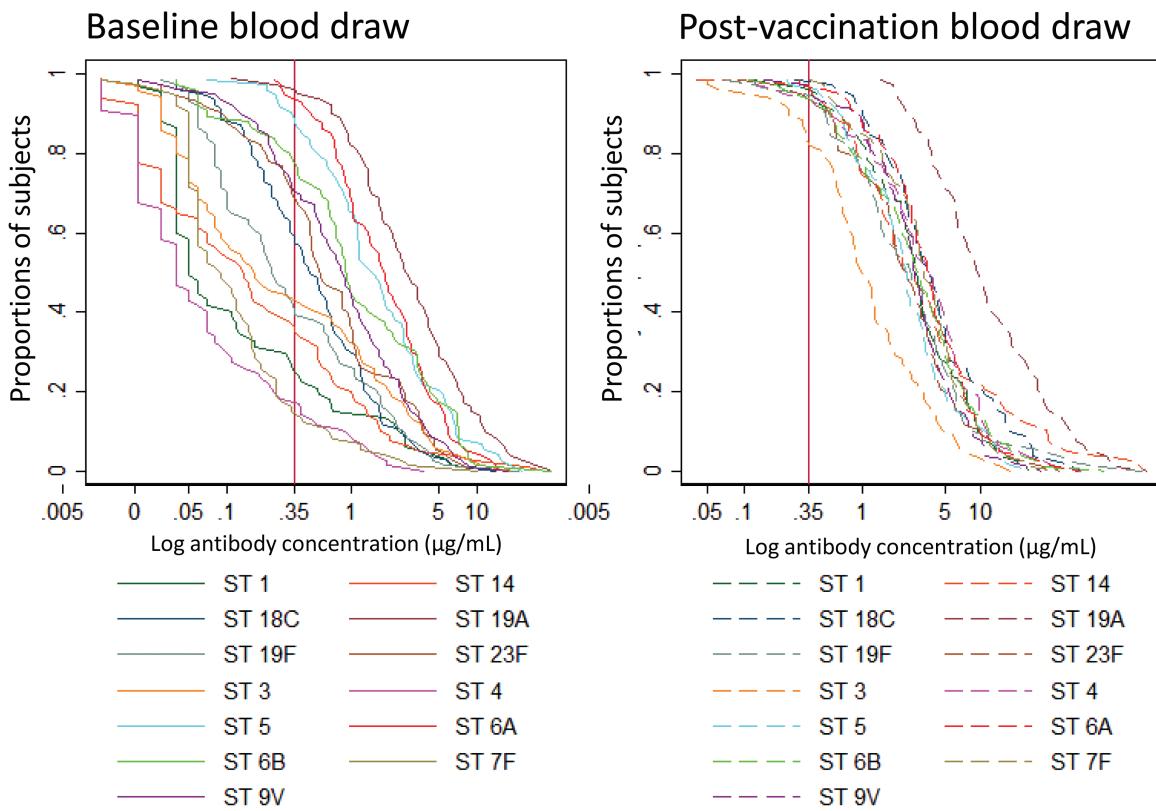
**Figure 1. Reverse cumulative distribution curves for serotype (ST)-specific immunoglobulin G (IgG) levels in the infant group according to study arm and blood draw time point.**



**Figure 2.** Reverse cumulative distribution curves for serotype (ST)-specific immunoglobulin G (IgG) levels in the toddler group according to study arm and blood draw time point.

In our study, a 2-dose primary series of PCV13 elicited a significantly lower antibody response than did a 3-dose series for 8 of 13 serotypes, a similar response for 4 serotypes (1, 5, 6A, and 7F), and a higher response for 1 serotype (19F). For comparison, in a systematic review and meta-analysis presented to the WHO's Strategic Advisory Group of Experts in October 2017 (see <http://www.who.int/immunization/sage/meetings/2017/>

october/3\_FULL\_PRIME\_REPORT\_2017Sep26.pdf?ua=1), which included 10 head-to-head studies of PCV dosing schedules, antibody GMCs after 2 primary doses were lower than after 3 primary doses for all except serotypes 19, for which they were similar (serotypes 4, 9V, and 18C were not analyzed). These differences in GMCs translated into differences in the proportions of infants with an IgG level of  $\geq 0.35 \mu\text{g/mL}$  for 5 serotypes (3,



**Figure 3.** Reverse cumulative distribution curves for serotype (ST)-specific immunoglobulin G (IgG) levels in the child group according to blood draw time point.

6B, 14, 18C, and 23F) in Burkina Faso but for only 3 serotypes (6A, 6B, and 23F) in the global meta-analysis. One month after the third vaccine dose in Burkina Faso, the 2 + 1 group had higher antibody levels than the 3 + 0 group for 9 of 13 serotypes, similar levels for 3 serotypes (4, 18C, and 19A), and lower antibody levels for serotype 3; differences in the proportions of subjects protected were found for only 2 serotypes (serotypes 3 [the 2 + 1 group had a lower proportion] and 5 [the 3 + 0 group had a lower proportion]). For comparison, in the global review, the 2 + 1 group had higher GMCs than the 3 + 0 group for all serotypes analyzed except for serotypes 3 and 19A, for which the GMCs were similar, but a higher proportion of the 2 + 1 group was protected than of the 3 + 0 group for serotypes 6B and 23F.

In a vaccine-effectiveness study in the United Kingdom, estimated correlates of protection against vaccine-type invasive pneumococcal disease varied according to serotype, from 0.14 µg/mL (for serotype 18C) to 2.83 µg/mL (for serotype 3) [30]. Therefore, the threshold of 0.35 µg/mL we used in our analysis might not be appropriate for certain serotypes or applicable to our setting and might have either underestimated or overestimated direct protection against clinical disease. In addition, no reliable correlates for protection against carriage, which drives the vaccine's herd effects, are available. In our setting, the 2 + 1 schedule likely provided good direct protection against invasive disease after the

booster dose, because the entire confidence interval for antibody GMC was above the highest of the thresholds estimated in the United Kingdom for 10 of 13 serotypes. However, given the intensity of pneumococcal transmission, several years of PCV use and high immunization coverage would be needed to achieve near elimination of vaccine serotypes and to limit the risk of disease among infants who have received only 2 doses. Thus, our comparative immunogenicity data do not provide sufficient evidence of superiority of 1 schedule over another; complementary information from a comparison of vaccine effects on carriage and invasive disease is needed to support decision making.

The WHO recommends that toddlers aged 12 to 23 months who have not been immunized receive 2 doses of PCV at least 2 months apart [19]. We found that 1 dose of PCV13 elicits a strong immune response in this age group; ≥90% of the participants achieved the serological correlate of protection for all except serotypes 3, 6B, and 23F. Therefore, in populations with low routine immunization coverage, including refugee populations, 1 dose provided as a catch-up vaccine for children aged 1 to 4 years would provide substantial health benefits.

Our results show that immune responses are similar between schedules within Burkina Faso, and Burkinabé infants and children respond as well or better to the vaccine than reference European or US populations; as a consequence, our data

do not indicate a superiority of 1 schedule over another. The initial choice of schedules will depend on estimates of overall indirect and direct population impact combined with financial and programmatic considerations; the final decision on schedules will depend on results from monitoring disease impact in vaccinated and unvaccinated populations and adjusting the schedules accordingly.

## Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

## Notes

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